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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,273	09/06/2001	George N. Cox	4152-2-PUS	2405

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EXAMINER
HAMUD, FOZIA M

ART UNIT	PAPER NUMBER
1647	13

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File copy

Office Action Summary	Application N .	Applicant(s)	
	09/889,273	COX ET AL.	
	Examiner	Art Unit	
	Fozia M Hamud	1647	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of the invention of Group I (claims 1-25 and 29-31) in Paper No.12, filed on 22 May 2003 is acknowledged.

Applicants' first ground of traversal is that since this Application is a national stage application, the regulations of 37 CFR 1.475((d) apply. Accordingly, Groups I and II are linked by the corresponding special technical feature of producing a soluble protein having a free cysteine, which should include the products having free cysteines produced thereby, as well as methods that make use of the free cysteine. Also Group I should not be separated from Groups III-IV, since Groups III-IV represent processes of using the protein of Group I. Applicants' second ground of traversal is that in the event that the claims of Group I are found allowable, they reserve the right to amend the claims of Groups III-IV to be commensurate in scope with the product and request that the amended claims be rejoined with the allowed claims.

The first ground of traversal is not found persuasive, because The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The method of producing a soluble protein having a free cysteine is not itself an advance over the prior art because Braxton (U.S. Patent 5,766,897, 06/1998) describes a methods and compositions for the production of soluble proteins having a free cysteine, (see column 37, lines 1-8). Because neither the

process nor product is novel and do not share a special technical feature, the groups do not relate to a single inventive concept.

With respect to Applicants' second ground of traversal, Applicants' elected group I is drawn to a method of producing a soluble protein having a free cysteine, in the event where this method is found allowable, product claims will be rejoined as long as the product claims do not precipitate new rejections.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 26-28 are withdrawn from consideration by the Examiner as they are drawn to non-elected inventions.

Claim rejections-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2a. Claims 8-14, 20-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case is not commensurate in scope with the claims drawn a "derivative or an antagonist thereof" of a growth hormone super-gene family or a method of producing said derivative or antagonist.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Instant specification does not define the structure of the derivatives or antagonists of growth hormone super-gene family, and, therefore, one of ordinary skill in the art would not know how to transfect a host cell in order for it to produce the desired compound. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise

definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore the written description in this case is not commensurate in scope with the claims drawn a "derivative or an antagonist thereof" of a growth hormone super-gene family or a method of producing said derivative or antagonist.

Claims 9-12 are rejected under 35 U.S.C. 112, first paragraph, insofar as they depend on claim 8 for the limitation set forth directly above.

2b. Claims 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 18 is drawn to the method of claim 1, further comprising attaching a cystiene-reactive moiety to said isolated protein to form a cysteine modified protein, however, once the cysteine free protein produced in the method of claim 1 is exposed to a cysteine blocking agent, all of the sylfhydryl groups of the free cysteine would be oxidized, therefore, no other cysteine-reactive moiety could be attached to said protein. With respect to claim 19 since all of the sylfhydryl groups of the free cysteine would be oxidized by the cysteine blocking agent, polyethylene glycol can not be also attached to the protein produced in the method of claim 1.

Therefore, applicants have not provided guidance to enable the method of claims 18-19, because Applicants have not shown that cystiene-reactive moiety can be

attached to proteins that have been exposed to a cysteine blocking agent, and one of ordinary skill in the art would not predictably be able to make said attachments to said protein.

Claim rejections-35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3a. Claims 1-25 and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable Braxton (U. S. Patent 5,766,897) or Cox et al (WO 95/32003) in view of Seely et al (EP 0 312 358).

Braxton discloses method and compositions for the production of soluble proteins that have a free cysteine residue present in either the naturally occurring protein or introduced by site specific mutations, and a method of attaching PEG to said proteins, (see abstract and column 11, lines 39-65, column 12, lines 1-6, table 1A on column 12).

Cox et al disclose IGF mutiens having free cysteine by substituting or adding a cysteine in the amino acid sequence of native IGF, said muteins which also have PEG attached at the free cysteine through a thiol-specific activating group, (abstract, page 6, lines 510 and claims). The IGF muteins disclosed by Cox et al have improved pharmacological and biological properties, (see page 37, table 6).

However, neither Braxton nor Cox disclose a method of producing a soluble protein having a free cysteine by exposing a host cell expressing said protein to a cystiene blocking agent, wherein the cystiene blocking agent forms a mixed disulfide with at the least one cysteine residue and isolating the soluble protein from the host cell.

Seely et al disclose a method of producing high yield of bioactive monomeric protein by exposing a host cell expressing said protein with an oxidizing agent, such as cystine, and isolating said protein, (abstract, column 3, 1-65).

Therefore, it would have been obvious at the time the instant case was filed to combine the teachings of Braxton or Cox et al with the teachings of Seely et al and define a method of producing a soluble protein having a free cysteine by exposing a host cell that expresses said protein with a thiol-reactive compound such as cystine to bind to the free cystiene, because both Braxton and Cox teach a method of producing proteins having a free cystiene residue and Seely et al teach that the exposure of host cells expressing recombinant proteins with cystine results in the production of high yield bioactive monomeric proteins.

With respect to claims 20-24 which recite specific EC_{50} concentrations and specific site where the PEG moiety is attached, it would have been obvious to a person

having ordinary skill in the art to use the method of Cox et al to modify the site of PEG attachment. Furthermore, combining the method taught by Cox et al with the method of Seely et al would have been expected to result in the production of proteins with improved EC_{50}, because Seely et al teach that exposing host cells expressing proteins with a thiol-reactive compounds yields highly active proteins and Cox et al disclose pegylated IGF muteins with reduced ED_{50} compared to unpegylated IGF mutein, (see Cox et la page 32, lines 18-25).

One of ordinary skill in the art would have been motivated to design a process of producing soluble and long acting recombinant proteins, because there is strong need in the art to develop stable proteins that are user friendly.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M Hamud whose telephone number is (703) 308-8891. The examiner can normally be reached on Monday, Wednesday-Thursday, 6:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4227 for regular communications and (703) 308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit 1647
23 July 2003

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